UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DT

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/705,587	11/03/00	Y.YU	Z ISPH-0500

EXAMINER	
GOLDBERG, I	
ART UNIT	**PAPER NUMBER**
1655	8

HM12/1108

JANE MASSEY LICATA
LICATA & TYRELL PC
66 E MAIN STREET
MARLTON NJ 08053

DATE MAILED: 11/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/705,587	Applicant(s) Y.YU ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Please note that the location and examiner handling the application has changed.

2. This action is in response to the papers filed September 11, 2001. Currently, claims 1-11 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-11 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for detecting or quantitating but the final process step is detecting. Therefore the claims are unclear as to whether the method is a method of detecting and quantitating or merely a method of detecting.

B) Claim 11 is indefinite because it is unclear how a method of detecting an oligonucleotide has any relation to administering the oligonucleotide exogenously.

Exogenously as defined by Webster is "derived or developed from external causes. It is unclear what this claim is intended to mean.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1, 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Impraim et al (US Pat. 6,228,578, May 2001).

Impraim et al (herein referred to as Impraim) teaches a method for detecting an oligonucleotide in a bodily fluid by contacting the fluid with a probe complementary to said oligonucleotide, wherein the probe comprises a detectable marker and a binding moiety (b) placing the fluid in contact with a solid support to which a binding partner of said binding moiety is attached (c) contacting said fluid with a single strand specific nuclease to degrade the non-hybridized oligonucleotides and (d) detecting a label associated with the marker. Impraim specifically detecting a non-radioactive hybridization assay for detecting of genetic defects, microbial infections or viral

infections (abstract). The sample, such as blood, is incubated with nucleic acid probes specific for target nucleic acids (limitations of Claim 1a)(abstract, col. 5, line 1). The hybrids are captured onto a solid phase, such as a test tube or polystyrene bead, coated with an anti-hybrid antibody (limitations of Claim 1b)(abstract, col. 5, lines 9-12). The unhybridized probe is eliminated with an enzyme, such as RNAase, that degrades non-hybridized probe (limitations of Claim 1c)(abstract, col. 4, lines 42-45). And finally the bound hybrid is detected using labels such as an enzyme, fluorescent molecule or a biotin-avidin conjugate (limitations of Claim 1d, 9) (abstract, col. 5, lines 37-39). The method is clearly illustrated in Figure 1. Impraim teaches that the method provides a cost-effective, sensitive, non-radioactive hybridization assay for the detection and quantification of nucleic acids in a sample (col. 4). Further the hybridization assay provides an assay in which sample preparation is simple and rapid, does not involve extractions, precipitation, centrifugation, or other purification methods (col. 4). Additionally, the method provides a non-radioactive hybridization assay having minimal false positives, allows accurate quantitative monitoring test for the level of microbial or viral infections (col. 4). Therefore, since Impraim has taught every limitation of the claimed invention, Impraim anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 3, 8, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Temsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Impraim et al (US Pat. 6,228,578, May 2001).

Temsami et al (herein referred to as Temsami) teaches a method for the quantification of oligonucleotide phoshorothioates in biological fluids and tissues. Temsami teaches a method which uses membrane-bound oligodeoxynucleotide phosphorothioate and then hybridized with labeled complementary oligonucleotides and exposed to X-ray film. Temsami teaches that the sensitivity of detection allows monitoring of pharmacokinetics of oligonucleotides in bodily fluids. Temsami teaches using digoxigen as a chemiluminescent method for detecting a label (limitations of Claim 8)(page 56).

Temsami does not specifically teach forming hybrids prior to contacting with a solid support, nor teaches using a nuclease to degrade non-hybridized probes.

However, Impraim et al (herein referred to as Impraim) teaches a method for detecting an oligonucleotide in a bodily fluid by contacting the fluid with a probe complementary to said oligonucleotide, wherein the probe comprises a detectable marker and a binding moiety (b) placing the fluid in contact with a solid support to which a binding partner of said binding moiety is attached (c) contacting said fluid with a single strand specific nuclease to degrade the non-hybridized oligonucleotides and (d) detecting a label associated with the marker. Impraim specifically detecting a non-radioactive hybridization assay for detecting of genetic defects, microbial infections or viral infections (abstract). The sample, such as blood, is incubated with nucleic acid probes specific for target nucleic acids (limitations of Claim 1a)(abstract, col. 5, line 1). The hybrids are captured onto a solid phase, such as a test tube or polystyrene bead, coated with an anti-hybrid antibody (limitations of Claim 1b)(abstract, col. 5, lines 9-12). The unhybridized probe is eliminated with an enzyme, such as RNAase, that degrades non-hybridized probe (limitations of Claim 1c)(abstract, col. 4, lines 42-45). And finally the bound hybrid is detected using labels such as an enzyme, fluorescent molecule or a biotin-avidin conjugate (limitations of Claim 1d, 9) (abstract, col. 5, lines 37-39). The method is clearly illustrated in Figure 1. Impraim teaches that the method provides a cost-effective, sensitive, non-radioactive hybridization assay for the detection and quantification of nucleic acids in a sample (col. 4). Further the hybridization assay provides an assay in which sample preparation is simple and rapid, does not involve

extractions, precipitation, centrifugation, or other purification methods (col. 4). Additionally, the method provides a non-radioactive hybridization assay having minimal false positives, allows accurate quantitative monitoring test for the level of microbial or viral infections (col. 4).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Temsmani with the method of Impraim. The ordinary artisan would have recognized the explicit benefits of the method of Impraim and would have been motivated to have monitored the pharmaokinetics of oligonucleotides with phosphorothioates. There would have been a reasonable expectation of success that a method of forming hybrids prior to the attachment to the solid support would work given the teachings of Impraim. Both Impraim and Temsamani teach that their method is useful for monitoring of nucleic acids. Thus, the ordinary artisan would therefore have recognized that the probe may be either attached to the solid support prior to the hybridization with the oligonucleotide or a hybrid may be formed followed by attachment to a solid support. Further, the ordinary artisan would have been motivated to have removed unhybridized probes with a nuclease for the expected benefit of removing the probes from the solution and to eliminate any interference.

9. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Temsami (Analytical Biochemistry, Vol. 215, page 54-58, 1993) in view of Impraim et al (US Pat.

6,228,578, May 2001) as applied to Claims 3, 8 above, and further in view of de Serres et al (Analytical Biochemistry, Vol. 233, pages 228-233, 1996).

While Impraim teaches sampling from blood and Temsami teaches sampling serum. Neither Temsami nor Impraim specifically teaches sampling from plasma.

However, de Serres teaches a method of determining plasma concentrations of a compound 4003W94, a 15 base phophorothioate antisense deoxyribonucleotides that is currently under preclinical evaluation for the treatment of restenosis following coronary artery angioplasty.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Temsami in view of Impraim to sample plasma. The ordinary artisan would be motivated to sampled plasma for monitoring the concentration of antisense molecules.

10. Claims 4-5, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Impraim et al (US Pat. 6,228,578, May 2001) in view of Lind et al (Nucleic Acids Research Vol. 26, No. 16, pages 3694-3699, 1998).

Impraim et al (herein referred to as Impraim) teaches a method for detecting an oligonucleotide in a bodily fluid by contacting the fluid with a probe complementary to said oligonucleotide, wherein the probe comprises a detectable marker and a binding moiety (b) placing the fluid in contact with a solid support to which a binding partner of said binding moiety is attached (c) contacting said fluid with a single strand specific nuclease to degrade the non-hybridized oligonucleotides and (d) detecting a label

associated with the marker. Impraim specifically detecting a non-radioactive hybridization assay for detecting of genetic defects, microbial infections or viral infections (abstract). The sample, such as blood, is incubated with nucleic acid probes specific for target nucleic acids (limitations of Claim 1a)(abstract, col. 5, line 1). The hybrids are captured onto a solid phase, such as a test tube or polystyrene bead, coated with an anti-hybrid antibody (limitations of Claim 1b)(abstract, col. 5, lines 9-12). The unhybridized probe is eliminated with an enzyme, such as RNAase, that degrades non-hybridized probe (limitations of Claim 1c)(abstract, col. 4, lines 42-45). And finally the bound hybrid is detected using labels such as an enzyme, fluorescent molecule or a biotin-avidin conjugate (limitations of Claim 1d, 9) (abstract, col. 5, lines 37-39). The method is clearly illustrated in Figure 1. Impraim teaches that the method provides a cost-effective, sensitive, non-radioactive hybridization assay for the detection and quantification of nucleic acids in a sample (col. 4). Further the hybridization assay provides an assay in which sample preparation is simple and rapid, does not involve extractions, precipitation, centrifugation, or other purification methods (col. 4). Additionally, the method provides a non-radioactive hybridization assay having minimal false positives, allows accurate quantitative monitoring test for the level of microbial or viral infections (col. 4).

Impraim does not specifically teach incorporating a 2'-O-methoxyethyl- modified nucleotide into the oligonucleotide.

However, Lind teaches that the 2' sugar-substituted o'(2-methoxyethyl) (MOE) has increased nuclease resistance and a very high binding affinity. The MOE-

substituted oligonucleotides have shown outstanding promise as antisense agents in several disease states and are presently being investigated in clinical trials for treatment of CMV retinitis. Lind further teaches that "one of the biggest advantages of the MOE substitution is the improvement in binding affinity, which is greater than many similar 2' modifications".(page 2694, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Impraim for detecting nucleic acids with a modification at the 2' position of at least one sugar moiety. The ordinary artisan would have readily realized that the modification at the 2' position would allow for improved binding affinity and nuclease resistance, which is ideal in hybridization assays such as the assay taught by Impraim.

11. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Impraim et al (US Pat. 6,228,578, May 2001) in view of Prosnyak et al (Genomics, Vol. 21, page 490-494, 1994).

Impraim et al (herein referred to as Impraim) teaches a method for detecting an oligonucleotide in a bodily fluid by contacting the fluid with a probe complementary to said oligonucleotide, wherein the probe comprises a detectable marker and a binding moiety (b) placing the fluid in contact with a solid support to which a binding partner of said binding moiety is attached (c) contacting said fluid with a single strand specific nuclease to degrade the non-hybridized oligonucleotides and (d) detecting a label associated with the marker. Impraim specifically detecting a non-radioactive

hybridization assay for detecting of genetic defects, microbial infections or viral infections (abstract). The sample, such as blood, is incubated with nucleic acid probes specific for target nucleic acids (limitations of Claim 1a)(abstract, col. 5, line 1). The hybrids are captured onto a solid phase, such as a test tube or polystyrene bead, coated with an anti-hybrid antibody (limitations of Claim 1b)(abstract, col. 5, lines 9-12). The unhybridized probe is eliminated with an enzyme, such as RNAase, that degrades non-hybridized probe (limitations of Claim 1c)(abstract, col. 4, lines 42-45). And finally the bound hybrid is detected using labels such as an enzyme, fluorescent molecule or a biotin-avidin conjugate (limitations of Claim 1d, 9) (abstract, col. 5, lines 37-39). The method is clearly illustrated in Figure 1. Impraim teaches that the method provides a cost-effective, sensitive, non-radioactive hybridization assay for the detection and quantification of nucleic acids in a sample (col. 4). Further the hybridization assay provides an assay in which sample preparation is simple and rapid, does not involve extractions, precipitation, centrifugation, or other purification methods (col. 4). Additionally, the method provides a non-radioactive hybridization assay having minimal false positives, allows accurate quantitative monitoring test for the level of microbial or viral infections (col. 4).

Impraim does not specifically teaches using a modified base such as 5-methylcytosine.

However, Prosnyak et al (herein referred to as Prosnyak) teaches that 5-methylcytosine is a modification that increases duplex stability. An oligonucleotide

which contains 5-methylcytosine is shown to bind DNA more specifically than the corresponding unmodified oligonucleotide.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the detection method of Impraim to include a modified base such as 5-methylcytosine for the expected benefit taught by Prosnyak. The ordinary artisan would be motivated to substitute a 5'methylcytosine in order to create a more stable duplex for detection purposes.

12. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Impraim et al (US Pat. 6,228,578, May 2001) in view of Lundin (Nucleic Acids Research, Vol. 25, No. 12, page 2535-2536, 1997).

Impraim et al (herein referred to as Impraim) teaches a method for detecting an oligonucleotide in a bodily fluid by contacting the fluid with a probe complementary to said oligonucleotide, wherein the probe comprises a detectable marker and a binding moiety (b) placing the fluid in contact with a solid support to which a binding partner of said binding moiety is attached (c) contacting said fluid with a single strand specific nuclease to degrade the non-hybridized oligonucleotides and (d) detecting a label associated with the marker. Impraim specifically detecting a non-radioactive hybridization assay for detecting of genetic defects, microbial infections or viral infections (abstract). The sample, such as blood, is incubated with nucleic acid probes specific for target nucleic acids (limitations of Claim 1a)(abstract, col. 5, line 1). The hybrids are captured onto a solid phase, such as a test tube or polystyrene bead,

coated with an anti-hybrid antibody (limitations of Claim 1b)(abstract, col. 5, lines 9-12). The unhybridized probe is eliminated with an enzyme, such as RNAase, that degrades non-hybridized probe (limitations of Claim 1c)(abstract, col. 4, lines 42-45). And finally the bound hybrid is detected using labels such as an enzyme, fluorescent molecule or a biotin-avidin conjugate (limitations of Claim 1d, 9) (abstract, col. 5, lines 37-39). The method is clearly illustrated in Figure 1. Impraim teaches that the method provides a cost-effective, sensitive, non-radioactive hybridization assay for the detection and quantification of nucleic acids in a sample (col. 4). Further the hybridization assay provides an assay in which sample preparation is simple and rapid, does not involve extractions, precipitation, centrifugation, or other purification methods (col. 4). Additionally, the method provides a non-radioactive hybridization assay having minimal false positives, allows accurate quantitative monitoring test for the level of microbial or viral infections (col. 4).

Impraim does not specifically teaches using S1 nuclease as the single-stranded specific nuclease.

However, Lundin teaches use of S1 nuclease to degrade single-stranded DNA.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Impraim to use S1 nuclease to degrade single-stranded DNA. The ordinary artisan would be motivated to have substituted a single-stranded DNA nuclease for RNAase when the probes used are DNA. Since, the ordinary artisan would be motivated to degrade any non-hybridized

probes, any nuclease which accomplishes this purpose would be an obvious substitute since they are functional equivalents.

Conclusion

13. No claims allowable over the art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Starianopoulos (US Pat. 5,989,809, November 1999) and Leying et al. (US Pat. 6,136,531, October 2000) teach methods of forming a hybrid nucleic acid prior to adding to a solid support (col. 7 of Starianopoulos and Figure 7 of Leying).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
October 26, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600